Development of L862, an Innovative Pulmonary Hypertension Treatment Targeting TRPC3/6

Principal Investigator

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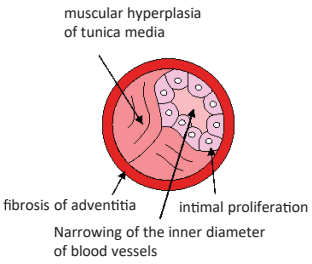
Project Outline

Pulmonary arterial hypertension (PAH, designated as an intractable disease)

• It is a condition in which the pulmonary arteries become abnormally narrowed and stiffened, resulting in increased pulmonary artery pressure. Symptoms such as shortness of breath and dyspnea appear with light movements.
• The number of patients in Japan is approximately 4,200 (FY 2020) and increasing every year. The global market size is projected to be USD 9.34 billion by 2034 (Research and Markets).
• The prognosis of PAH associated with systemic sclerosis is particularly poor, and unmet medical needs are still high.
• PAH is caused by pulmonary artery remodeling (intimal proliferation, muscular hyperplasia of tunica media, and fibrosis of adventitia), and existing oral vasodilator drugs are not effective in treating PAH associated with advanced lesions, venous disease, and collagen diseases such as systemic sclerosis.
→ Oral drugs that can directly intervene in remodeling are needed.

Vascular remodeling In PAH patients



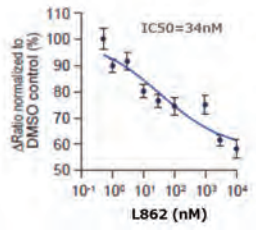
About TRP (Transient Arterial Potential) C3/6

• TRP channels are membrane proteins that exist on lipid membranes and form a superfamily of 28 types.
• They form tetramers and function as non-selective cation channels by permeating Na and Ca ions.
• It acts as a sensor to detect various extracellular signals.
• Various evidences that TRPC3/6 is involved in PAH and remodeling (Kuwahara et.al. JCI 2006; 116: 3114, etc.).
→ TRPC3/6 inhibitors may be therapeutic agents directly involved in PAH remodeling.

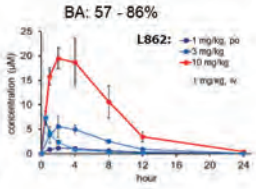
L862, Novel TRPC3/6 inhibitor

- L862 inhibits TRPC3/C6 channels at low concentrations and exhibits high selectivity for other proteins.
- L862 shows excellent physicochemical properties, and PK/safety profiles, with no manufacturing concerns.
- The substance patent application (WO2019208812) has been granted in JP, US, EP, and CN.
- Use Patent applications for heart failure, acute kidney injury, and so on containing L862 were filed.
- At a PMDA face-to-face consultation, we received confirmation that the nonclinical studies submitted for the physician-initiated Phase 1 clinical trial were adequate and that the proposed Phase 1 clinical trial protocol was acceptable.

Inhibition of TRPC6

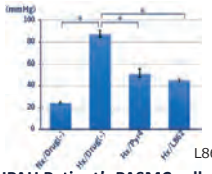


PK Profiles in Rats

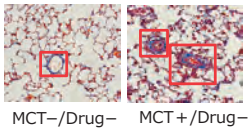


Effects of L862 on PAH model rats and patient-derived pulmonary arterial smooth muscle cells

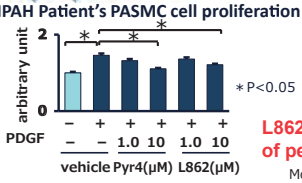
Monocrotaline induced PAH model Rats
systolic pulmonary arterial pressure

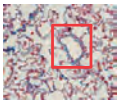


Monocrotaline-induced PH rats (Masson-Trichrome Staining)



IPAH Patient's PASMC cell proliferation





L862 administration suppressed fibrosis of perivascular tissues in the PH model.
Moriuchi, Kuwahara et al. in preparation 2021

L862 improves pulmonary hypertension in various established animal models of PAH.

Target disease: Pulmonary arterial hypertension
Current status: GLP-preclinical studies have been completed and Execution of a P1 clinical trial is under preparation.
Description of technology: Oral small molecule therapeutic agent for PAH based on a novel mechanism of action
Contact for inquiries regarding joint research and licensing: Department of Medical Innovation, The University of Osaka Hospital, Ms. Sasajima, Email: michiyo.sasajima@dmi.med.osaka-u.ac.jp